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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1639	30

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/361,576	STOCKWELL ET AL.	
	Examiner	Art Unit	
	My-Chau T. Tran	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/21/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-81 and 83-104* is/are pending in the application.

4a) Of the above claim(s) *84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-81,83 and 85-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Note: The examiner for your application in the PTO has changed. However, the Group and/or Art Unit location of your application in the PTO is remained the same, which is Group Art Unit 1639.

Status of the Claims

1. In previous Office Action (mailed 12/18/2002), the previous examiner stated that the new claims 82-128 are renumbered as claims 57-103 because the entry of these claims occurred without the prior entry of claims 57-81 (e.g. cancellation of claims 57-81). And applicant has renumbered these claims (e.g. claims 82-128) at the request of the previous examiner.

2. Applicant's amendment filed 5/21/03 in Paper No. 29 is acknowledged and entered. Claim 82 is canceled by the amendment. Claims 57-81 and 83-103 are amended by the amendment. Claim 104 is added by the amendment.

3. Claims 57-81 and 83-103 are pending.

Election/Restrictions

4. Claim 84 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 26.

5. Claims 57-81, 83, and 85-104 are treated on the merit in this Office Action.

Withdrawn Rejections

6. The previous rejections 35 USC 112, second paragraph, for claims 57-61, 63-81, 83, and 85-103 have been withdrawn in view of applicant's amendments of claims 57-81 and 83-103 and cancellation of claim 82.

7. The previous rejection under 35 USC 102(a) as being anticipated by Juan et al. Experimental Cell Research 239:104-110 (February 1988) for claims 57-62, 64-67,69-83, 85-88, 102, and 103 have been withdrawn in view of applicant's amendments of claims 57 and 58 (e.g. the added limitation of "*wherein the plurality of reaction vessels comprises at least 96 reaction vessels*").

8. The previous rejection under 35 USC 102(a) as being anticipated by Claycomb U.S. Patent No. 6,316,207 B1 November 2001 (PCT published May 1998) for claims 57-62, 64-67,69-83, 85-88, 102, and 103 have been withdrawn in view of applicant's amendments of claims 57 and 58 (e.g. the added limitation of "*wherein the plurality of reaction vessels comprises at least 96 reaction vessels*").

9. The previous rejection under 35 USC 102(e) as being anticipated by Walsh, U.S. Patent 5,990,092 (November 1999) for claims 57-62, 69-78, 83, 85-88, 102, and 103 have been withdrawn in view of applicant's amendments of claims 57-62, 69-78, 83, 85-88, 102, and 103.

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 112

11. Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62 recites a limitation on a "*third ligand*," which is not required in claim 58 from which claim 62 depends.

Response to Arguments

12. Applicant's argument directed to the above rejection under 35 U.S.C. 112, second paragraph, for claim 62 has been fully considered but they are not persuasive for the following reasons.

Applicant contends that "[a]ntecedent basis of "*third ligand*" can be implicitly found in step g of claim 58 in the language "*wherein seconds are thirds*". The language is intended to mean that every occurrence of the word "second" in steps d-f is replaced with the word "third".

Applicant's arguments are not convincing since the language of "*wherein seconds are thirds*" does not implicitly refers the term "second ligand" but would also refers to the "second step" of the method or the "second compound". Therefore, there is no antecedent basis of the term "*third ligand*". It is suggested that applicant amend the language "*wherein seconds are thirds*" to "*wherein* the *second ligand* ~~are~~ is *third ligand*" to clearly define the intended meaning of the claim term and would clearly provide antecedent basis for the term "*third ligand*".

Claim Rejections - 35 USC § 102

13. Claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102-103, and 104 (*include new claim 104*) are rejected under 35 U.S.C. 102(b) as being anticipated by Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997).

The Photiou et al. reference discloses a method for evaluating the in vitro antiproliferative activity (inhibiting cell replication and therefore DNA synthesis) of drugs as single agents and as combinations using human melanoma cell lines G361 and StMl11a (abstract). Page 465, column 1, discloses an indirect immunofluorescence method in which cells are seeded on glass coverslips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabbit anti-tubulin antibodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC. Page 466, columns 1 and 2, discloses the interpretation of the tubulin immunofluorescence data, including the intracellular localization of the primary and secondary antibodies. The prevention of tubulin polymerization is a "post-translational event" and an "intracellular biochemical reaction." Accordingly, the Photiou et al. reference anticipates present claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102, and 103.

Response to Arguments

14. Applicant's argument directed to the above rejection under 35 USC 102(b) as being anticipated by Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997) for claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102-103, and 104 was considered but they are not persuasive for the following reasons.

Applicant alleges that Photiou et al. does not teach "[t]he cell-based assays in question can be carried out in high-throughput format (e.g. with 96 or higher reaction vessels)". Therefore, Photiou et al. do not anticipates the presently claimed invention.

Applicant's arguments are not convincing since Photiou et al. do disclose a cell-based assay can be carried out in a high-throughput format. Photiou et al. disclose that 'cells were seeded at 3000 cells/well/100 µl in a 96-well plates' (pg. 464, right col., lines 13-21). Therefore, Photiou et al. do anticipate the presently claimed invention.

Claim Rejections - 35 USC § 103

6. Claims 89-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one or more of Walsh, U.S. Patent 5,990,092 (November 1999); Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997); Juan et al. Experimental Cell Research 239:104-110 (February 1988); Claycomb, U.S. Patent No. 6,316,207 B1 (November 2001) and the Final Conference Program of LabAutomation'98 held in San Diego, CA January 17-21, 1998, pages 99, 100, 124, 129, and 212.

The teachings of the Walsh, Photiou et al., Juan et al., and Claycomb references are described in the corresponding rejections under 35 U.S.C. 102 above and are incorporated herein in their entirety.

The Walsh patent, Example 4, discloses an in vitro assay for selecting GATA-6 molecules that modulate vascular smooth muscle proliferation. Column 28, lines 28-44, discloses that A7r5 cells (rat) are cultured in media containing the test molecule for up to 72 hours. The cells are harvested at various time points and the proliferative state of the cells is

determined by immunohistochemical assays including a BrdU assay and a proliferating cell nuclear antigen (PCNA) assay (i.e. an assay for an intracellular antigen). Column 28, lines 47-51, discloses that cells are fixed onto a tissue culture dish (reaction vessel), dried, and immunostained using a monoclonal antibody to PCNA (i.e. first ligand). Column 27, lines 13-25, discloses that the BrdU assay involves adding BrdU (a reagent known to exert an effect on the process of proliferation) to growth media (containing the cells to be tested) for 24 hours, fixing and permeabilizing the cells, and identifying proliferating cells with a mouse anti-BrdU antibody coupled to FITC (i.e. a second ligand coupled to a fluorescent tag). One of skilled in the art would know that washing steps to remove unbound antibody are inherently a part of immunostaining assays. *This reference was discuss in the previous Office Action in the rejection under 35 USC 102(e).*

The Photiou et al. reference discloses a method for evaluating the in vitro antiproliferative activity (inhibiting cell replication and therefore DNA synthesis) of drugs as single agents and as combinations using human melanoma cell lines G361 and StMl11a (abstract). Page 465, column 1, discloses an indirect immunofluorescence method in which cells are seeded on glass coverslips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabbit anti-tubulin antibodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC. Page 466, columns 1 and 2, discloses the interpretation of the tubulin immunofluorescence data, including the intracellular localization of the primary and secondary antibodies. The prevention of tubulin polymerization is a "post-translational event" and an "intracellular biochemical reaction." *This reference was discuss in the previous Office Action in the rejection under 35 USC 102(b).*

The Juan et al. reference discloses a method for monitoring the phosphorylation status of the retinoblastoma susceptibility gene product (protein) pRb, the phosphorylation of which is the key event committing the cell to enter the S phase of the cell cycle (abstract). Page 105 (Materials and Methods) discloses that human peripheral blood lymphocytes were treated with PHA to stimulate proliferation. The cells were assayed using one or more of three different antibodies by immunocytochemical methods. Fixed cells were incubated with anti-pRb^T mAb conjugated to Cy-Chrome and/or anti-pRb^{P-} mAb conjugated to FITC. In addition, fixed cells were incubated with anti-cyclin D3 mAb, washed, and incubated with FITC-conjugated goat anti-mouse IgG antibody. Page 109, column 1, last paragraph, discloses that the assay "*can be conveniently used to rapidly screen activity*" of antitumor agents. Additionally, the reference discloses that the phosphorylation state of pRb can be correlated with DNA replication by detecting BrdU incorporation. *This reference was discuss in the previous Office Action in the rejection under 35 USC 102(a).*

The Claycomb patent discloses mouse cardiac cell line and associated cell culture system for testing cardiac drugs *in vitro* (abstract). Column 10, example 2, discloses that cells are labeled BrdU. Fixed cells are treated nuclease/anti-5-bromo-2'-deoxyuridine, washed, and incubated with peroxidase-conjugated anti-mouse antibody. The bound secondary antibody is developed using diaminobenzidine and visualized by the resulting blue-black staining. Column 6, lines 35-63, discloses that the cells are also assayed using primary antibodies to desmin and myosin heavy chain and secondary goat anti-mouse antibody conjugated to FITC. *This reference was discuss in the previous Office Action in the rejection under 35 USC 102(a).*

The cited references do not explicitly teach test compounds from a combinatorial library, the release of test compounds from a solid support, or various capacities and densities of wells in well plates.

With respect to combinatorial libraries as test compounds as well as the release of test compounds from solid supports, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to use members of combinatorial libraries as test compounds, including those made on solid supports which would require their release before testing. One would have been motivated to do so because combinatorial libraries were primarily synthesized as leads for drug development to be tested for biological activity and solid-phase synthesis was the most common method of combinatorial library synthesis practiced at the time.

With respect to particular numbers of wells, their capacities, and arrangements within a plate, for example, it would have been well within the abilities of one of ordinary skill to select well array formats from those commonly sold for the purpose of high throughput screening as described ion pages 99, 100, 124, 129, and 212 of the Final Conference Program of LabAutomation'98, which include 1536-well, 384-well, 96-well, and 10,000-well formats, for example. Well volumes and spacings include 12 microliters and 2.25 mm, for example.

Response to Arguments

15. Applicant's argument(s) directed to the above rejection under 35 USC 103(a) as being unpatentable over any one or more of Walsh, U.S. Patent 5,990,092 (November 1999); Photiou et al. European Journal of Cancer 33(3):463-470 (March 1997); Juan et al. Experimental Cell Research 239:104-110 (February 1988); Claycomb, U.S. Patent No. 6,316,207 B1 (November 2001) and the Final Conference Program of LabAutomation'98 held in San Diego, CA January

17-21, 1998, pages 99, 100, 124, 129, and 212 for claims 89-101were considered but they are not persuasive for the following reasons.

Applicant argues that "[t]he "Final Conference Program of LabAutomation '98" references teaches that "*some cell-based assays remain difficult to automate due to the incompatibility of traditional assay platforms with robotics*" (see page 159, first paragraph). Therefore, applicant argues that "Final Conference Program of LabAutomation '98" references *teaches away* from the presently claimed invention, in that it fails to convey to one of ordinary skill in the art the desirability to combine the teachings of the cited references and a reasonable expectation of success in such a combination."

Applicant's arguments are not convincing since the Final Conference Program of LabAutomation'98 reference does not teach away from the presently claimed invention. Page 159 (cited by applicant) refers the problem of automating a specific type of cell-based assays that is permeable-membrane cell-based assays. However, the second paragraph provides the resolution of such an assay by the development of an automation-compatible 24-well cell culture membrane insert system. Further, the Final Conference Program of LabAutomation'98 reference teach that high-throughput screening assays in 96-well or 1536-well plates provide advantages in both cost and speed. For example, page 99 recite that "[M]iniaturization of conventional high-throughput screening assays to the 1 microliter scale in 1536-well plates affords significant advantages in both cost and speed". Thus one of ordinary skill in the relevant art would have been motivated to combine the teachings of the cited references to achieve the presently claimed invention because there is reasonable expectation of success (e.g. significant advantages in both

cost and speed). Therefore, the combine teaching of the cited references do teach the presently claimed invention.

New Rejections – Necessitated by Amendment

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 57-81, 83, and 85-104 are rejected under 35 U.S.C. 102(e) as being anticipated by Taylor (US Patent 6,103,479).

Taylor discloses methods of performing high throughput screening of physiological response of cells to biological active compounds (col. 6, lines 40-47). The method analyzes cells interactions with drug, protein, ligand, or other substances that either binds with the surface expressed moieties of cells or that is taken up by the cells (col. 13, lines 37-56; col. 14, lines 5-9). The method comprises preparing an array of cells, contacting the array of cells to a fluid delivery system to enable reagent (e.g. drugs or other substances) delivery to the array of cells (col. 4, lines 44-48), conducting high-throughput screening by acquiring an image of the entire array of cells to detect signals from all wells at once to identify wells that exhibit a response, converting the signals into digital data and utilizing the digital data to determine the distribution,

environment or activity of the cells (col. 13, lines 37-56; col. 19-20, Example 2). The format of the array comprises a standard microtiter plate format such as 96 well plates or 384 well plates (col. 6, lines 3-18). Therefore, the method of Taylor anticipates the presently claimed method.

The features of remaining independent and dependent claims are either specifically described by the reference (e.g. the volumes of the vessels or the numbers of vessels), or constitute obvious variations in parameters which are routinely modified in the art (e.g. repeating step a of claim 58), and which have not been described as critical to the practice of the invention.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 703-305-6999.

The examiner is on Increased Flex Schedule and can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 703-306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

mct
September 4, 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER